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The Fundamental Characteristics of Pyrazinamide: A Review

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ABSTRACT

Pyrazinamide (PZA) is an important drug used for the treatment of tuberculosis (TB). It is full of characteristic sterilizing activity, and when added to regimens containing rifampicin (RMP,R). It becomes more effective bacilli during the initial intensive phase of chemotherapy, thus duration of chemotherapy get's shortened from 9 months to 6 months. Despite its remarkable in vivo activity, PZA is not active enough against Mycobacterium tuberculosis under usual conditions at close to pH 7. Later on it has been observed that PZA is not known to show any bactericidal action in the first two days of treatment.

Keywords: Pyrazinamide, M. tuberculosis, Chemotherapy.

INTRODUCTION

Pyrazinamide play a unique role in shortening the therapy from previously 9-12 months to 6 months,[1-4] because it kills a population of semidorment tubercle bacilli in acidic pH environment that are not killed by other TB drugs.[1]It is unconventional drug[2]. Despite its remarkable sterilizing activity in vivo,[3,4] Pyrazinamide is not active against mycobacterium tuberculosis under "normal" culture conditions near neutral pH,[5] The action of pyrazinamide has been proposed to be the result of a weak acid effect of pyrazinoic acid on the tubercle bacilli[2,6]. Unlike conventional antibiotic, which are more active against the bacteria, Pyrazinamide is exactly the opposite, that is, it is less active against young growing tubercle bacilli but is more active against old non-growing bacilli.[7] In this study we present preparation, standardization and

evidence that pyrazinoic acid and pyrazinamide could de-energize the membrane by collapsing the membrane potential and the membrane transport function at acid pH as a mechanism of action.[8, 9]

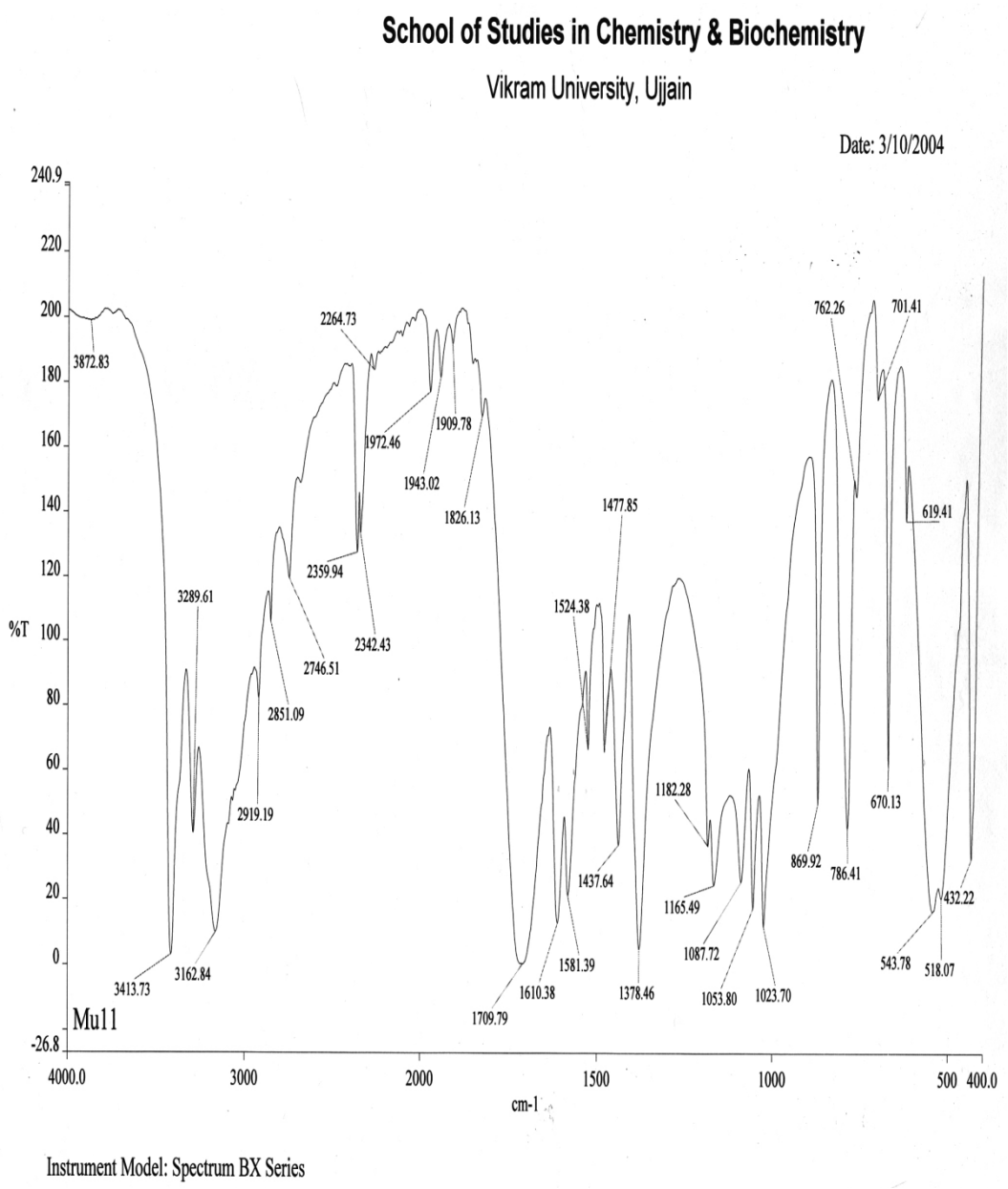

TABLE 1.1
Interpretation of IR-Spectrum of pyrazinamide

Peak name	Intensity cm^{-1}	Assignment
A	3413.73 (sharp)	Primary amide N-H stretching (dil solution)
B	3162.84 (sharp)	N-H stretching (Symmetrical)
C	2359.94(Weak)	C=N Stretching of the Ring
D	1709.79 (sharp)	
E	1581.39 (median)	N-H in Plane-bending (II).
F	1378.46 (median)	Coupled C-N Stretching (III)
G	1053.80 (Sharp)	N-H in plane bending
H	869.92 (median)	Aromatic C-H out of plane bending
I	786.41 (median)	Aromatic C-C out of plane bending.
J	670.13 (median)	OCN bending of the – $CONH_2$ grp (IV)

MATERIALS AND METHODS

Preparation part include paste formation by dissolving sodium benzoate I.P & P.V.P K 30 I.P in 1 lit purified water, similarly dissolve 2 lit of purified water in starch I.P with continue stirring. Now both the solution was allowed to mix with stirring and cool this paste at room temperature, now raw material is mixed with the paste, it is passed through mesh no. 8 on granulater thus obtained granules are dried in air for 10 min . Later on blending is made and then it is compressed on 16 station rotatary machine with breakline and lower punchase plain. Pyrazinamide was characterized by FTIR perkin Elmer (BX70836) Spectrophotometer. The characteristics peaks obtained are shown in table 1.1.

Growth of mycobacteria

M. tuberculosis strain H37Ra was grown in 7H9 Liquid medium (Difco) supplemented with (ADC) AT 37^0C for various times ranging from a few weeks to a few months with occasional agitation.

Effect of rotenone & azide on pyrazinamide activity

The strain culture of M. tuberculosis as cultivated above, harvested by centrifugation washed in one volume of PBS (pH 7.0) and resuspended in citrate buffer (pH 6.0) cells were treated with sodium azide (1.5mm) and with rotenone (5 um) as well as with pyrazinamide (50 mg/L), Rotenone, sodium azide in combination with pyrazinamide for 0 to 7 days.

RESULTS

Prepared pyrazinamide material is subjected to IR spectrum analysis for it's identification the obtained spectrum is signed for it's details as illustrated in the following table [1.1] and spectra.

Rotenone and azide, which inhibits membrane bound cytochrome c oxidase and reduces generation of membrane potential by decreased protein pumping, all increased the activity of pyrazinamide against M. tuberculosis.

CONCLUSIONS

Probably it is the least understood of all the anti-tuberculosis drugs. PZA is an unconventional and paradoxical drug. The study of PZA continues to give us new surprises.The aim should be the initial selection of potential molecules for their activity against slow- growing persiters. Improved understanding of how PZA works is likely to provide insights into the biology of the tubercle bacillus, help to design new sterilizing drugs that will kill the "persisters" more effectively and shorten the duration of chemotherapy.

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